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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No. 09/881,204	Applicant(s) DOMINKO ET AL.	
	Examiner Thai-An N. Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-119* is/are pending in the application.

4a) Of the above claim(s) *69,86-97 and 101-119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-68,70-85 and 98-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 and 12*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' Preliminary Amendment, filed 3/3/03, Paper No. 14, has been entered. Claims 1-47 have been cancelled. Claims 48-119 have been added.

Claims 48-119 are currently pending. Claims 48-68, 70-85 and 98-100 are under current examination.

Election/Restrictions

Applicant's election with traverse of Group I, originally claims 1-22, 44 and 45, now represented by claims 48-85 and 98-100, in Paper No. 14 is acknowledged. The traversal is on the ground(s) that the search of restriction groups I-XV does not impose a serious burden upon the Examiner, as search concerning the patentability of invention of one group [in particular, Group I], will clearly uncover art of interest to other groups. Applicants argue that because claims of Groups I-III have been classified in the same class and subclasses, and can therefore be examined without serious burden on the part of the Examiner. Applicants argue that the inventions in the Restriction requirement are not mutually exclusive and independent. Applicants believe that all of the claims of Inventions I-XV are related. See pp. 14-15 of the Response.

This is not found persuasive because each of the Inventions in Groups I-XV are directed to mutually exclusive and independent methods which require materially separate protocols and practice different methods steps. With regard to

same classification, it is noted that restriction is not based solely upon classification. It is reiterated that the inventions have acquired a separate status in the art as a separate subject for inventive effort and require independent searches. The search for each of the above inventions is not co-extensive particularly with regard to the literature search. Further, a reference which would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Accordingly, such a search would be considered undue. Furthermore, with regard to claim 69, it is noted that the specification teaches that mitochondria that would be used to enrich the cells would be from the same source as the donor [karyoplast]. As such, claim 69 would be grouped with Invention III [originally claims 1, 25-27 and 30, which are drawn to methods of generating a pluripotent mammalian cell, wherein the mitochondria is derived from the same species as the nuclear donor, are used to supplement the mitochondria in the hybrid cell. Accordingly, claim 69 would not be considered to be drawn to the elected invention and is thus withdrawn from consideration.

The requirement is still deemed proper and is therefore made FINAL.

Claims 69, 86-97 and 101-119 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 14.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

The disclosure is objected to because of the following informalities:

p. 9, [0021], line 2, the term *invention* is misspelled.

Appropriate correction is required.

Claim Objections

Claim 63 is objected to because of the following informalities: there is no comma between sheep and goat. Appropriate correction is required.

Claim 69 is objected to because of the following informalities: the term *mitochondria* is misspelled. Appropriate correction is required.

Claim 76 is objected to because the of the following informalities: the term *ionomycin* is misspelled in line 2 of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 62-65, 77 and 81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 62, as written, is vague. The claim recites that the cytoplast donor is "derived from" a non-human species. Thus, it is unclear if the cytoplast donor has changed, and in what way, from its original source, the non-human species. Claims 63 and 64 depend from claim 62.

Claim 63, as written, is vague. The claim recites that the cytoplast donor is "derived from mouse, rat, rabbit, sheep, goat, pig or cow." Thus, it is unclear if the cytoplast donor has been changed, and in what way, from its original source(s).

Claim 64, as written, is vague. The claim recites that the cytoplast donor is "derived from cow". Thus, it is unclear if the cytoplast donor has been changed, and in what way, from its original source, the cow.

Claim 65, as written, is vague. The claim recites that the nuclear donor is "derived from" various cells. However, it is unclear if the nuclear donor has been changed, and in what way, from its cell sources.

Claim 77, as written, is unclear. The claim recites that the donor nucleus is from an, "embryonic, fetal, or adult cell/karyoplast." It is unclear if "/" is meant to further limit or expand the claim. Furthermore, it is unclear if the karyoplast refers to only the adult karyoplasts, or also embryonic or fetal karyoplasts.

Claim 81, as written, is unclear. The claim recites that the donor nucleus is from a "differentiated stem cell". However, once a stem cell is differentiated, it is no longer considered a stem cell, as it would be a differentiated into various cell lineages and would thus be considered a differentiated cell.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 48, 54-67, 70-79, 81, 82, 84, 85 and 98-100 are rejected under 35 U.S.C. 102(b) as being anticipated by Campbell *et al.* [WO 97/07668, published 6 March 1997].

The claims are directed to a method of generating a hybrid mammalian cell comprising (a) preparing a cytoplast fragment from a mammalian oocyte or fertilized zygote [the cytoplast donor]; (b) preparing a cell with a donor nucleus or karyoplast with a donor nucleus [nuclear donor] which is taken from any mammalian species; and (c) fusing said cytoplast fragment with said cell or said karyoplast, thereby producing a hybrid mammalian cell [claim 48]. In further embodiments, the mammalian oocyte or fertilized zygote is enucleated [claim 54], the mammalian oocyte or fertilized zygote is enucleated by micromanipulation or

centrifugation in an appropriate gradient in the presence of a microfilament inhibitor [claim 55], the mammalian oocyte is matured *in vivo* [claim 56], the mammalian oocyte is matured *in vitro* [claim 57], the mammalian oocyte is selected from the group consisting of an activated low MPF oocyte, an aged, unactivated, low MPF oocyte, and an unactivated, high MPF, metaphase II oocyte [claims 58-59], wherein the cytoplast donor is a different species from that of the nuclear donor [claim 60], wherein the cytoplast donor is from the same species as that of the nuclear donor [claim 61], wherein the cytoplast donor is derived from a non-human mammalian species: mouse, rat, rabbit, sheep, goat, pig or cow [claims 62-63], where the cytoplast donor is derived from a cow [claim 64], wherein the nuclear donor is derived from various cell types [claim 65], wherein the nuclear donor cell is a karyoplast and is an interphase cell [claims 66-67], wherein the fusion of the cytoplast fragment with the nuclear donor is mediated by electrical fusion, chemical fusion, viruses, liposomes, or cell surface proteins [claims 70-72], wherein the method further comprises an activation step that occurs before or after the fusion step [claims 73-76], wherein the donor nucleus is from an embryonic, fetal, or adult cell/karyoplast [claim 77], wherein the donor nucleus is from a diploid cell [claim 78], wherein the donor nucleus is from a differentiated or undifferentiated stem cell, or differentiated or undifferentiated somatic cell [claims 81-82], wherein the donor nucleus has been genetically modified [claims 84-85]. The claims are further

directed to populations of hybrid cells produced by the claimed method [claims 98-100].

Campbell *et al.* teach methods of reconstituting an animal embryo by transferring a diploid nucleus into an oocyte that has been arrested at the metaphase of the second meiotic division. They teach that the diploid nuclear donor can be donated by a cell in G0 or G1 phase of the cell cycle at the time of transfer; after reconstitution, the embryo is then activated. See *Abstract*. In particular, Campbell teaches that oocytes arrested at metaphase II can give rise to viable embryo if normal ploidy is maintained and if the embryo is not activated at the time of NT. See p. 4, lines 27-32. They teach that the methods can be used in any animal, and in particular can be used in non-human mammals such as ungulates [cattle, sheep, goats, water buffalo, camels and pigs] but can also be used in animals such as horses, rats, mice or rabbits. See p. 5, lines 14-28.

Campbell teach a method, wherein a diploid nucleus is transferred from a donor into an enucleated recipient oocyte. This donor nucleus can be genetically modified [see pp. 5-7]. Nuclear donors may be fully or partially differentiated cells, or undifferentiated cells that can be cultured *in vitro*, or abstracted *ex vivo* [see p. 8, lines 13-17]. Campbell teaches that the oocytes used in the method can be matured either *in vitro* or *in vivo* [see p. 9, lines 2-5]. The techniques to enucleate the oocyte are described, for example, by physical manipulation [see p. 10, lines 12-16]. After enucleation, the donor nucleus is introduced into the oocyte by either fusion or

injection to the recipient cells. Campbell teaches that three established methods of inducing fusion are by exposure to chemicals that promote fusion [*e.g.*, polyethylene glycol], the use of an inactivated virus [such as a Sendai virus], or by electrical fusion. See p. 11, lines 1-25. Campbell teaches that the fusion of an oocyte/karyoplast couplet is preferably by electropulsing [see p. 12, lines 1-8]. After fusion, the resulting reconstituted oocyte can then be activated, for example by electrical pulses [see p. 13]. Campbell particularly teaches that bovine oocytes were used in the described methods of nuclear transfer and primary fibroblasts synchronized in the G0 phase were used as nuclear donors. See Example 1.

Accordingly, Campbell anticipates the claimed invention.

Claims 48, 54, 55, 58, 59, 61-64, 66, 70, 71, 73, 74, 76-82, 98-100 are rejected under 35 U.S.C. 102(b) as being anticipated by Campbell *et al.*, [**Biol. Of Reprod.**, 49:933-942 (1992), Document AS4 in IDS filed 10/18/02, Paper No. 12].

Campbell teach methods of nuclear transfer, wherein nuclear transfer embryos which were reconstructed at different times following activation were examined. See p. 934, 2nd column, 2nd ¶. In particular, cumulus oocyte complexes were isolated from cows, oocytes were then isolated and fertilized by spermatozoa incubation. Embryos were then sorted by developmental stage and selected for synchronization into G1/S or G2 cell cycle stages; cleaved embryos were transferred to M2 medium until use [p. 935, 1st column, *Embryo Culture and Synchronization*].

Matured oocytes were stripped of cumulus cells and washed in activation medium, transferred to an activation chamber and given a single pulse to activate [p. 935, 1st column, *Electrical Activation of In Vitro-Mature Bovine Oocytes*]. Oocytes were then enucleated by stripping the cumulus cells, culturing the oocytes in a medium containing cytochalasin B and enucleation was carried by aspiration. The oocytes were then transferred to a manipulation chamber, where a blastomere was inserted under the zona pellucida of the enucleated oocyte; the couplet was then transferred to an activation chamber and fused by a single electrical pulse [p. 935, col. 1-2, bridging ¶]. The oocytes, activated oocytes and nuclear transfer embryos were then morphologically examined.. Campbell teach that all nucleic, regardless of cell cycle stage, undergo DNA replication when transplanted into metaphase II cytoplasts with high MPF [maturation-promoting factor]. See *Abstract*.

Accordingly, Campbell *et al.* anticipate the claimed invention.

Claims 48, 54-59, 61-67, 70, 71, 73, 75-82, 84, 85 and 98-100 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolf *et al.* [**Journal of Biotechnology**, 65:99-110 (1998)].

Wolf teach methods of nuclear transfer in mammals, which involves the transfer of genetic material from a donor cell [karyoplast] to the cytoplasm of an oocyte or zygote from which genetic material has been removed [cytoplast]. See Figure 1. Wolf teach that many factors influence the efficiency of embryo cloning,

such as methods for activation of oocytes, cell-cycle coordination between donor cell and recipient cytoplast, methods of fusion between the donor and cytoplast. See *Abstract*. They teach the efficiency of nuclear transfer in different species using embryonic cells as nuclear donors [Table 1], the efficiency of nuclear transfer in different species using cultured cells as nuclear donors [Table 2]. Wolf discuss various factors that affect the efficiency of nuclear transfer, such as synchronization between the donor and recipient [see p. 102-103, bridging ¶]. Further, it is taught that nuclear transfer can be used to produce transgenic animals which can then used as bioreactors for human proteins, organs, etc. which can be used in various therapies. See pp. 105-106.

Accordingly, Wolf anticipate the claimed invention.

Claims 48, 54-57, 61-64, 66, 67, 70-74, 76-79, 81, 82 and 98-100 are rejected under 35 U.S.C. 102(b) as being anticipated by Susko-Parrish *et al.* [U.S. Pat. No. 5,496,720, published March 5, 1996].

Susko-Parrish teach methods of nuclear transfer in cows. They teach the parthenogenic activation of oocytes which can then be used for nuclear transfer. In particular, they teach mature metaphase II oocytes are collected from cows, or immature oocytes can be collected and matured *in vitro*. Prior to activation, the cumulus cells are stripped from the oocytes. The oocyte is then introduced into a medium that causes the introduction of free calcium ion into the oocyte cytoplasm,

this can be effected by processes known in the art such as the use of an ionophore such as ionomycin or electric shock. See col. 6, lines 44-64. The oocytes are the subjected to an inhibitor of phosphorylation, such as DMAP. See col. 7, lines 25-29. Susko-Parrish teach that the oocytes are enucleated and then parthenogically activated by the described method [col. 8, lines 53-61]. The oocytes can then be fused by electrofusion, for example, or by polyethylene glycol [col. 9, lines 13-45].

Accordingly, Susko-Parrish anticipate the claimed invention.

Claims 48, 54-57, 61-64, 66-68, 70-73, 75-79, 81, 82 and 98-100 are rejected under 35 U.S.C. 102(b) as being anticipated by Sims *et al.* [U.S. Pat. No. 5,453,366, published September 26, 1995].

Sims teach methods of cloning mammalian embryos by transferring a nucleus from a donor mammalian embryo to an enucleated recipient oocyte and culturing the nuclear transferred bovine embryo. See *Abstract*. In particular, Sims teach methods of transferring a donor membrane-bounded nucleus isolated from a donor bovine embryo, the embryo being at a stage of development where significant cell differentiation has not occurred, to a recipient metaphase II bovine oocyte and culturing the NT embryo *in vitro*. See col. 3-4, bridging ¶. The nucleus of the donor embryo should only be membrane bround, which can consist of an entire blastomere, or may consist of a karyoplast, which is an aspirated cellular subset including a nucleus and a small amount of cytoplast bounded by a plasma

membrane. Col. 5, lines 42-47. The oocyte can either be collected matured *in vivo*, or be matured *in vitro.* Mature oocytes can be treated with cytochalsin B to allow enucleation by micromanipulation. See col. 7, lines 19-62. The enucleated oocytes are then activated and then the donor nucleus can be transferred into the recipient enucleated oocyte. The resulting nuclear transfer embryo can then be fused, by electrofusion or polyethylene glycol, for example, see col. 8-9. The resulting embryo can then be activated by exposure to an ionophore such as ionomycin [col. 9, lines 12-18].

Accordingly, Sims anticipates the claimed invention.

Claims 48, 54-60, 62-67, 70, 71, 75-78, 81-85 and 98-100 are rejected under 35 U.S.C. 102(b) as being anticipated by Robl *et al.* [WO 98/07841, published 26 February 1998, Document AP1 in IDS filed 10/18/02, Paper No. 12].

Robl teach methods of nuclear transfer involving transplantation of a donor cell into enucleated oocytes of species different from the donor cell. The resulting NT units can then be used to produce human isogenic embryonic or stem cells. See *Abstract.* Robl teach that the human embryonic or stem cells (which can be genetically modified) can be used in treatments by cell transplantation. See p. 5, lines 21-25; pp. 7-8. Robl teaches that the nucleus of a human cell (e.g., an adult differentiated human cell) can be transplanted into an enucleated animal oocyte [see p. 9, lines 18-28]. They particularly teach that the nucleus of a human

epithelial cell was transferred into a bovine oocyte, nuclear transfer was effected and the resulting cell was cultured, which gave rise to human stem-like or embryonic cells [p. 10, lines 10-18]; however, any type of human or animal cells may be used in the method [see p. 12, lines 6-16]. The oocytes may be matured *in vitro* or *in vivo* [p. 13, lines 1-16]. The metaphase II oocyte is then enucleated by methods known in the art, such as incubation in cytochalasin B, or by microsurgical enucleation [p. 14, lines 10-24]. The single human or animal cell is then transferred into the perivitelline space of the enucleated oocyte to produce the NT unit. The cells can then be fused, by methods such as electrofusion or by a virus [p. 15, lines 1-16]. The resulting NT unit can then be activated by an ionophore or by electric shock, for example [p. 16, lines 10-20]. The activated NT units can then be cultured *in vitro* to generate cell colonies.

Accordingly, Robl *et al.* anticipate the claimed invention.

Claims 48-57, 60-64, 66, 67, 70, 71, 72-74, 77, 78, 81, 82 and 98-100 are rejected under 35 U.S.C. 102(b) as being anticipated by Peura [WO 98/29532, published 9 July 1998].

Peura teach methods of nuclear transfer utilizing oocytes which are free of their zona pellucida. They teach that the oocytes may be matured *in vitro* or *in vivo* [pp. 4-5]. The cytoplast may be prepared by any method that results in the enucleation, for example dissection, aspiration, centrifugation [p. 10, lines 24-28].

Embryonic donor cells may be obtained by any source, for example bovine, and at any stage of development [p. 11, lines 2-10]. In particular, Peura teach the development of bovine nuclear transfer embryos. Cytoplasts were produced by removing zona pellucida of *in vitro* matured bovine oocytes by (1) incubation in 0.5% pronase, followed by (2) incubation in medium supplemented with cytochalasin B, and then (3) enucleation of the cytoplasts. The cytoplasts were then activated by ionophore exposure for use in NT. Zona-free donor bovine embryos were then fused to the enucleated cytoplasts by electrofusion. The reconstituted embryos were then cultured and analyzed. See Example 6.

Accordingly, Peura anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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